DETAILED ACTION

Response to Arguments

Applicants argue over the 35 USC 103 rejection over Tofovic that the rejection is erroneous because the reference does not teach treatment of drug-induced nephrotoxicity. Applicants present an argument from a text on nephrology in which different sections are written for renal injury and also for drug nephrotoxicity and conclude that there would be no need for the distinction if the mechanism for all kidney diseases were the same. Applicants present various arguments to the effect that the treatment for nephrotoxicity will not necessarily be the same. Applicants admit that such disorders such as proteinuria may also occur by nephrotoxicity. Applicants feel that the burden of proving that the proposed modification of the prior art has a reasonable expectation of success has not been met.

In response to the above arguments, it is still the stance of the Office that regardless of how the kidney disease originated, it would be obvious that the treatment would effectively treat kidney disease regardless of if it is drug-induced or naturally occurring. Unless there is data to contradict this, it remains obvious that treatment of a kidney disease whether it is drug-induced or naturally occurring will be effectively treated by the same medications. As discussed in the previous Office Action, the reference by Prescott teaches that the main differences between nephropathies and nephrotoxicity is that conventional clinical investigation of renal function is of limited value in nephrotoxicity.

Regarding the reference provided by Applicants, it is noted that the CsA drug was found to decrease proteinuria in nephrotic patients and was also found to decrease proteinuria in nephrotic patients previously treated with cytotoxic drugs.

Applicants argue over the 35 USC 103 rejections over Xiao et al. and Tofovic and Xiao in view of Allison that the pathologies of the kidney are not the same across a wide-variety of kidney diseases, including nephrotoxicity. Applicants present many of the same arguments as presented above and those arguments have been addressed. Applicants also argue that Xiao et al. teaches away from the instant invention because it teaches that 2-hydroxyestradiol does not induce NO synthesis and would not protect against the progression of renal disease.

In response to the above arguments over Xiao et al., it is once again noted that Xiao et al. teaches that estradiol stimulates endothelial cell-derived NO synthesis and that decreased NO synthesis is associated with the pathogenesis of renal disease. However, this information relates to estradiol and not its metabolites. Xiao et al. teaches that the estradiol metabolites are effective at inhibiting GMC growth by inhibiting DNA synthesis, collagen synthesis and cell proliferation (second paragraph, Figures 4 and 5) and the authors conclude that the metabolites may prevent glomerulosclerosis by the inhibition of abnormal growth of GMC's. Therefore, the metabolites are more effective than estradiol at inhibiting growth of GMC's.

Accordingly, the rejections are maintained and are given below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. "Renoprotective effects of 2-hydroxyestradiol", *J Am Soc Nephrol* 12: 86A, 2001.

Tofovic et al. teach that chronic treatment with 2-hydroxyestradiol (2-OHE) significantly reduced symptoms of nephropathy, such as proteinuria (meeting the limitations of claims 5-6 and 8), glomerulosclerosis (meeting the limitation of claims 9-10 and 12), and interstitial inflammation (meeting the limitation of claims 13-14 and 16) in male obese rats, which is a model of nephropathy (see entire abstract).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Tofovic et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. One having ordinary skill in the art would have been motivated to extend the teachings of Tofovic et al. to treat various forms of nephropathies with estradiol metabolites because the prior art

teaches that an estradiol metabolite is effective at treating various types of nephropathies.

Claims 1-2, 4-6, 8-10, 12-14, 16-18, 20-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao, S. et al. "Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth", Hypertension, 2001; 37; 645-650.

Xiao et al. teach that the growth of glomerular mesangial cells (GMC) is associated with the pathogenesis of renal diseases (Pg. 645, second paragraph). It is further taught that estradiol and its hydroxy and methoxy metabolites inhibit glomerular mesangial cell (GMC) growth by inhibiting DNA synthesis, collagen synthesis (meeting the limitations of claims 21-22 and 24), and cell proliferation (meeting the limitations of claims 17-18 and 20; pg. 647, second paragraph and Figures 4 and 5). The authors conclude that estradiol metabolites may prevent glomerulosclerosis by this inhibition of abnormal growth of GMC's (further meeting the limitation of claims 9-10 and 12; pg. 648, first paragraph). It is further taught that the hydroxy and methoxy metabolites of estradiol are more potent than estradiol at inhibiting the growth of GMC's (pg. 647, second paragraph and Figures 4 and 5).

Regarding the conditions cited in claims 1, 2, 9, 13, 17, and 21, it is considered that these conditions are all associated with nephropathy; therefore, it is obvious that the teachings of Tofovic et al. would treat the conditions listed in the above claims.

Xiao et al. does not teach that the conditions listed in claims 1, 2, 9, 13, 17, and 21 are drug-induced; however, these pathologies of the kidney would display the same symptoms regardless of if it is drug-induced or a natural occurrence, so the treatment with estradiol metabolites would have the same results. Because the prior art teaches that estradiol metabolites are renoprotective in cells modeling renal pathogenesis, one having ordinary skill in the art would have been motivated to extend the findings of Xiao et al. to *in vivo* models of nephropathies to evaluate the renoprotective effects of these compounds.

Claims 3, 7, 11, 15, 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofovic et al. and Xiao et al. as applied in the above rejections and in view of Allison et al. (U.S. Pg-Pub 2006/0083778).

Tofovic et al. and Xiao et al. do not teach a controlled release formulation.

Allison et al. teach sustained release formulations of estradiol metabolites, including 2-hydroxyestradiol, 2-methoxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol (meeting the limitations of claims 3, 7, 11, 15, 19, and 23; paragraph 0007, 0008, 0010).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Tofovic et al. and Xiao et al., which teach that estradiol metabolites induce renoprotective effects with Allison which teaches sustained drug delivery of estradiol metabolites. One having ordinary

skill in the art would have been motivated to formulate controlled release delivery of estradiol metabolites in an extended release drug delivery device to maintain therapeutic blood levels.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617